REMARKS

Claims 1-5 are pending for examination.

Sequence Listing

The Examiner requested that Applicants provide a paper copy of the Sequence Listing with the present response. Applicants provide the requested paper copy of the Sequence Listing herewith.

Utility

Claims 1-5 were rejected on the assertion that the claimed subject matter lacks utility. The Examiner cites Hu et al. as teaching that a skilled artisan would consider the precise level of PRO1864 gene expression as relevant. With respect to the Kuo reference, which was submitted in support of Applicants' position that Hu's microarray data is not relevant, the Examiner asserts that it cannot be ascertained if Kuo's microarray data was consistent or inconsistent with Kuo's RT-PCR data. According to the Examiner, Kuo's poor correlation between microarray and proteomic expression profiles does not speak to changes in mRNA attributable to disease - independent differences between samples. The Examiner asserts that the good correlation between mRNA and protein expression was found after treatment with the potent immunostimulating agent CpG while it is not clear what effect, if any, CpG treatment will have on PRO1864 mRNA and polypeptide levels.

The Examiner further maintains that the present application only measures mRNA and presumes that PRO1864 polypeptide levels will track with the changes in PRO1864 mRNA without providing any evidence of how PRO1864 polypeptide levels change in melanomas compared to normal skin. The Examiner asserts that the specification does not disclose any biological activity or function for the PRO1864 polypeptide.

With respect to the first Declaration of Mr. Grimaldi, the Examiner asserts that several of the statements therein are conclusory and unsupported. According to the Examiner, it is unknown what level of difference is being reported or how many samples were tested. The Examiner asserts that Mr. Grimaldi's Declaration does not provide anything specific concerning PRO1864 mRNA expression, PRO1864 polypeptide expression, or the correlation between the two in tumor tissue and normal tissue. The Examiner maintains that there is no evidence

concerning the normal range of PRO1864 mRNA levels or PRO1864 polypeptide levels in normal tissue or tumor tissue and that there is no evidence that a normal range of PRO1864 mRNA or PRO1864 polypeptide levels could be defined that would distinguish normal tissue from tumor tissue. According to the Examiner, without knowledge of the variation within the pool one would not know if any particular measurement from a tissue would indicate normal tissue or tumor tissue.

The Examiner asserts that the skilled artisan would not know if or how expression of the PRO1864 polypeptide would change in tumors because there are numerous levels of control of protein synthesis, degradation, processing and modification, which are only apparent by direct protein analysis. In support of this position, the Examiner cites Haynes, Molecular Biology of the Cell (third edition), Molecular Biology of the Cell (fourth edition), Genes VI, and the Meric reference.

The Examiner also maintains that the Polakis Declaration supports his position. With respect to the second Polakis Declaration, the Examiner asserts the data presented in Exhibit B scores mRNA and protein levels as either "+" or "–" and that the data are insufficient to support Applicants' assertion that an increase in mRNA levels corresponds with an increase in the level of the corresponding protein. According to the Examiner, while the Polakis Declaration refers to being able to quantitatively measure mRNA and protein levels in both tumor tissue and normal tissue, this data is not supplied. In addition to the Polakis Declaration, the Examiner cites Lian et al. and Fessler et al. as supporting his position that mRNA levels and protein levels are not correlated.

The Examiner maintains that the skilled artisan would not know if the reported change in PRO1864 transcripts is tumor-dependent or tumor-independent and would not know if or how PRO1864 polypeptide expression would change in cancer. In addition, the Examiner asserts that Applicants' utility standard would mandate only a showing that it is "not implausible" that the invention will work for its intended purpose.

With respect to the Orntoft and Futcher references submitted in support of Applicants' position, the Examiner asserts that it is unclear whether PRO1864 is abundantly expressed. In addition, with respect to Exhibits 1-22 submitted in support of Applicants' position, the Examiner asserts that these references do not relate to the PRO1864 protein.

Applicants incorporate by reference their previously submitted arguments, and for the reasons of record assert that the specification contains a disclosure of utility and therefore must be taken as sufficient to satisfy the utility requirement of 35 U.S.C. § 101. Applicants also submit that for reasons of record, the PTO has not met its burden of providing evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility. However even if the PTO has met its initial burden, Applicants' rebuttal evidence previously submitted and additional evidence submitted herewith is sufficient to prove that it is more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true. As stated previously, Applicants' evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. The standard is not absolute certainty.

Substantial Utility

Summary of Applicants' Arguments and the PTO's Response

Applicants' asserted utility rests on the following argument:

1. Applicants have provided reliable evidence that mRNA for the PRO1864 polypeptide is expressed at least two-fold higher in melanoma compared to normal skin tissue;

2. Applicants assert that it is well-established in the art that a change in the level of mRNA for a particular protein, *e.g.* an increase, generally leads to a corresponding change in the level of the encoded protein, *e.g.* an increase;

3. Given the differential expression of the PRO1864 mRNA in melanoma, it is more likely than not that the PRO1864 polypeptide is also differentially expressed in melanoma, making the claimed antibodies useful as diagnostic tools, alone or in combination with other diagnostic tools.

Applicants understand the PTO to be making two arguments in response to Applicants' asserted utility:

1. The PTO challenges the reliability of the evidence reported in Example 18, stating that Hu et al. cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and diseased tissue;

2. The PTO cites Haynes et al. to support its position that one of skill in the art would not know if the disclosed change in PRO1864 mRNA transcripts is associated with a corresponding change in the level of PRO1864 protein.

The PTO has Concluded that the data in Example 18 are Sufficient to Establish the Utility of the Claimed Invention

As an initial matter, Applicants point out that in other applications filed by Applicants that rely on data from *the exact same disclosure, Example 18*, and in which the Applicants have submitted *substantially the same references* in support of their asserted utility, the PTO has concluded that:

> "[b]ased on the totality of evidence of record, **one of skill in the art would find it more likely than not that an increase in message as measured by RTPCR would be predictive of an increase in protein expression levels,** absent evidence to the contrary. Therefore, the data presented in Example 18, which demonstrates differential expression of nucleic acids encoding PRO1180, also supports a conclusion of differential expression of PRO1180 polypeptide. Therefore, one of ordinary skill in the art would be able to use the PRO1180 polypeptide diagnostically for distinguishing normal kidney and rectal tumor tissues compared to kidney tumor and normal rectal tissue, as asserted by Applicant."

See *Examiners Reasons for Allowance* in pending Application No. 10/063,529. See also *Examiners Reasons for Allowance* in Application No. 10/063,530, No. 10/063,524, No. 10/063,582, and No. 10/063,583, all of which conclude that the data presented in Example 18, which demonstrate differential expression of the nucleic acids encoding certain PRO polypeptides, also support a conclusion of differential expression of the PRO polypeptides, making the claimed PRO polypeptides and antibodies that bind the PRO polypeptides useful for diagnostic purposes.

Applicants therefore request that the Examiner recognize the utility of the claimed invention, supported by the data presented in Example 18 and the numerous cited references, as was done in the other applications referenced above.

The Data Reporting Differential Expression of PRO1864 mRNA is Sufficient to Provide Utility for the mRNA as a Diagnostic Tool

Applicants next address the PTO's argument that the evidence of differential expression of the gene encoding the PRO1864 polypeptide in melanoma is insufficient, and that the

literature cautions against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue.

Applicants continue to maintain that the PTO's position that additional details regarding Example 18 are required to establish utility for the claimed antibodies is beyond that required under 35 U.S.C. §101. As previously submitted, Applicants' statement of utility is presumed to be true, and further evidence to establish utility should not be required. *See In re Langer*, 503 F.2d at 1391, 183 USPQ at 297; *In re Malachowski*, 530 F.2d 1402, 1404, 189 USPQ 432, 435 (CCPA 1976); *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995); *M.P.E.P.* §2107.02 (III). Requests for additional evidence should be imposed rarely, such as only when a statement is incredible in the light of the knowledge of the art, or factually misleading. *In re Citron*, 325 F.2d 248, 139 USPQ 516 (CCPA 1963). Applicants remind the Examiner that Applicants enjoy a presumption that their assertions are true. The Examiner must approach Applicants' assertion of utility as being sufficient to satisfy the utility requirement. M.P.E.P. §2107.02, "Procedural Considerations Related to Rejections for Lack of Utility," states:

> As a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope. *M.P.E.P. §2107.02* at III. A., *quoting In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (C.C.P.A. 1974) (emphasis in original).
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> Thus, *Langer* and subsequent cases direct the Office to presume that a statement of utility made by an applicant is true. ... Office personnel should not begin by questioning the truth of the statement of utility. Instead, any inquiry must start by asking if there is any reason to question the truth of the statement of utility. ... Clearly, Office personnel should not begin an evaluation of utility by assuming that an asserted utility is likely to be false, based on the technical field of the invention or for other general reasons. *Id.*

With respect to the use of the PRO1864 nucleic acid to distinguish tumor from normal tissue, the Examiner must accept this assertion as true "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility." Therefore, the question is whether the PTO has established that there is a reason to doubt the objective truth of Applicants'

assertion that using standard RT-PCR procedures to examine the expression of the PRO1864 mRNA in pooled normal skin tissue samples and pooled melanoma samples, Applicants discovered that PRO1864 mRNA is differentially expressed between normal and tumor such that it can be used as a diagnostic tool.

In addition, as previously submitted, the standard for establishing a utility is a low one, and statistical certainty is not required:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

This is further supported by the previously cited C.C.P.A. decision *Nelson v. Bowler*, 626 F.2d 853, 206 U.S.P.Q. 881 (C.C.P.A. 1980), in which the Court found that "a rigorous correlation is not necessary where the test for pharmacological activity is reasonably indicative of the desired response." *Id.* (emphasis added). The Court concluded that a "reasonable correlation" between the observed properties and the suggested use was sufficient to establish practical utility. *Id.* at 857 (emphasis added). In addition, the Court rejected the notion that the testing must be statistically significant to support a practical utility and recognized that qualitative data are acceptable demonstrations of utility. *Id.* at 855-857. Thus, the PTO's requirement that Applicants provide numerical precision and statistical certainty to establish utility is contrary to established standards for utility. Accordingly, these arguments do not support the PTO's position as they do not lead one skilled in the art to question Applicants' asserted utility.

The Examiner cites Hu et al. as teaching that a skilled artisan would consider the precise level of PRO1864 gene expression as relevant. With respect to the Kuo reference, which was submitted in support of the position that Hu's microarray data is not relevant, the Examiner asserts that it cannot be ascertained if Kuo's microarray data was consistent or inconsistent with Kuo's RT-PCR data. According to the Examiner, Kuo's poor correlation between microarray and proteomic expression profiles does not speak to changes in mRNA attributable to disease-

independent differences between samples. The Examiner asserts that the good correlation between mRNA and protein expression was found after treatment with the potent immunostimulating agent CpG while it is not clear what effect, if any, CpG treatment will have on PRO1864 mRNA and polypeptide levels.

Applicants have submitted the Kuo reference to demonstrate that there is a strong correlation between changes in mRNA levels detected using RT-PCR methodology and changes in levels of the encoded polypeptides. While Applicants find no basis in the Kuo reference to question whether or not the detected differences in mRNA levels were CpG-ODN dependent, Applicants maintain that this issue is not pertinent to the utility of the claimed antibodies because, as discussed herein, the methodology employed by Applicants is sufficient to demonstrate that variations in PRO1864 mRNA levels are disease-dependent. Accordingly, Applicants continue to maintain that the Kuo reference demonstrates the reliability of the RT-PCR methodology employed in the experiments of Example 18 to detect changes in mRNA levels and the strong correlation between the detected changes in mRNA levels and changes in the levels of the encoded polypeptides.

Applicants previously submitted a copy of a first Declaration of J. Christopher Grimaldi, an expert in the field of cancer biology. As discussed previously, the declaration explains the importance of the data in Example 18, and how differential gene and protein expression studies are used to differentiate between normal and tumor tissue.

In paragraphs 6 and 7, Mr. Grimaldi explains that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over- or underexpressed in tumor cells compared to corresponding normal tissue. He states that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. Thus, the results of Example 18 reflect at least a two-fold difference between normal and tumor samples. He also states that the results of the gene expression studies indicate that the genes of interest "can be used to differentiate tumor from normal," and that the samples were made from pooled samples of tumor and corresponding normal tissue, increasing the accuracy of the data, thus establishing their reliability. *See Grimaldi Declaration* at ¶¶ 5 and 7.

In addition, he explains that, contrary to the PTO's assertions, "[t]he precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue." *Grimaldi Declaration* at ¶7. Thus, since it is the relative level of expression between normal tissue and suspected cancerous tissue that is important, the precise level of expression in normal tissue is irrelevant, as is the baseline level of expression. As Mr. Grimaldi states, "[i]f a difference is detected, this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor." *Id.*

The Examiner asserts that Mr. Grimaldi's Declarations are unpersuasive because, "the assertions that 'Data from pooled samples is more likely to be accurate than data obtained from a sample from a single individual' (paragraph 5), 'it is reasonable to assume that any detectable differences seen between two samples will represent at least a two fold difference in cDNA' (paragraph 6), 'The precise levels of gene expression are irrelevant' (paragraph 7), and 'If a difference is detected, ... the gene and its corresponding polypeptide... are useful for diagnostic purposes' (paragraph 7) are conclusory and unsupported." *Office Action* at 6. The Examiner also maintains that the skilled artisan would not know if the reported change in PRO1864 transcripts is tumor-dependent or tumor-independent.

As an initial matter, Applicants submit that the Declaration of Mr. Grimaldi is based on personal knowledge of the relevant facts at issue. Mr. Grimaldi is an expert in the field and conducted or supervised the experiments at issue. Applicants remind the PTO that "[o]ffice personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned." PTO Utility Examination Guidelines (2001) (emphasis added). In addition, declarations relating to issues of fact should not be summarily dismissed as "opinions" without an adequate explanation of how the declaration fails to rebut the Examiner's position. *In re Alton* 76 F.3d 1168 (Fed. Cir. 1996). The PTO has not supplied any reasons or evidence to question the accuracy of the facts upon which Mr. Grimaldi based his statements. Mr. Grimaldi has personal knowledge of the relevant facts related to the data in Example 18, has based his statements on those facts, and the PTO has offered no reason or evidence to reject either the underlying facts or his statements. Therefore, the PTO should accept Mr. Grimaldi's statements that "any visually detectable difference seen between two samples is indicative of at

least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue" and that the genes of interest "can be used to differentiate tumor from normal." Together, these statements establish that there is at least a two-fold difference in expression, and that the results set forth in Example 18 are reliable enough that they can be used to distinguish tumor from normal tissue.

The Examiner provides no basis for dismissing these statements by Grimaldi. Hu cannot support the Examiner's dismissal of the first Grimaldi Declaration because it is silent regarding the use of differentially expressed genes as diagnostic tools in general, and the reliability of pooled samples in particular. In particular, Hu says nothing about whether or not differential expression in pooled samples is susceptible to disease-independent differences between samples and the Examiner has not offered any arguments or evidence to counter Grimaldi's statements. Therefore, Hu does not provide a basis for doubting Applicants' differential expression data. As such, there is no evidence that one skilled in the art would question whether the differential expression of PRO1864 mRNA in pooled samples was disease-dependent or disease-independent.

Furthermore, as stated in the first Grimaldi Declaration, the "detection of variations in gene expression is likely to represent a more generally relevant condition when pooled samples from normal tissues are compared with pooled samples from tumors in the same tissue type." *First Grimaldi Declaration* at ¶ 5. In particular, use of a pooled sample is a more accurate indication of whether an observed change is tumor-dependent than use of individual samples because the observed extent of differential mRNA levels between tumor tissue and normal tissue is normalized to reflect the typical degree of variation within the pool. In other words, should there be a particular sample in the pool which exhibits an atypical degree of variation between tumor tissue and normal tissue, the effects of that sample on the observed degree of variation are mitigated by the other members of the pool. Accordingly, the observation of differential mRNA expression in tumor tissue compared to normal tissue using pooled samples is a reliable indication that such differential expression is in fact disease dependent.

In conclusion, Applicants submit that the evidence reported in Example 18, supported by the first Grimaldi Declaration, establish that there is at least a two-fold difference in PRO1864 mRNA in melanoma compared to normal skin tissue. Therefore, the only issue which remains is

whether the data in Example 18 regarding differential expression of the PRO1864 mRNA are reasonably correlated with differential expression of the PRO1864 polypeptide such that the antibodies to the PRO1864 polypeptide have utility as diagnostic tools as well. As discussed below, even if the PTO has established a reasonable doubt regarding Applicants' assertion that they are reasonably correlated, Applicants' overwhelming rebuttal evidence is more than sufficient to establish that changes in mRNA level lead to corresponding changes in protein level.

The PTO's Evidence is Not Relevant to Determining Whether a Change in mRNA Level for a Particular Gene leads to a Corresponding Change in the Level of the Encoded Protein

Applicants turn next to the second portion of their argument in support of their asserted utility – that it is well-established in the art that a change in the level of mRNA encoding a particular protein generally leads to a corresponding change in the level of the encoded protein; given Applicants' evidence of differential expression of the mRNA for the PRO1864 polypeptide in melanoma, it is likely that the PRO1864 polypeptide is also differentially expressed; and proteins differentially expressed in certain tumors, and antibodies that bind such proteins, have utility as diagnostic tools. As stated above, the Examiner should approach these assertions of utility with a presumption that they are true.

The Examiner asserts that the present application only measures mRNA and presumes that PRO1864 polypeptide levels will track with the changes in PRO1864 mRNA without providing any evidence of how PRO1864 polypeptide levels change in melanomas compared to normal skin. According to the Examiner, the specification does not disclose any biological activity or function for the PRO1864 polypeptide.

As previously submitted Applicants maintain that, in general, differential mRNA expression correlates with differential expression of the polypeptide encoded by the mRNA. Accordingly, in view of the differential expression of the PRO1864 mRNA, it is more likely than not that the PRO1864 polypeptide will be differentially expressed. In addition, Applicants reiterate that, regardless of the biological activity or function of the PRO1864 polypeptide, its differential expression renders the claimed antibodies useful as diagnostic agents.

The Examiner asserts that the skilled artisan would not know if or how expression of the PRO1864 polypeptide would change in tumors because there are numerous levels of control of

protein synthesis, degradation, processing and modification, which are only apparent by direct protein analysis. In support of this position, the Examiner cites Haynes, Molecular Biology of the Cell (third edition), Molecular Biology of the Cell (fourth edition), Genes VI, and the Meric reference.

Applicants acknowledge that there are several mechanisms for regulating gene expression. However, as previously submitted, Applicants maintain that the predominant mechanism for regulating polypeptide levels is by regulating transcription.

The Examiner cites Lian et al. and Fessler et al. as supporting his position that mRNA levels and protein levels are not correlated.

With respect to the Lian reference, as an initial matter, Applicants note that the difference in the number of differentially expressed transcripts identified compared to the number of differentially expressed polypeptides identified is a consequence of the difficulty of identifying polypeptides by two dimensional gel electrophoresis and does not reflect a lack of correlation between differential mRNA expression and differential expression of the encoded polypeptide. In particular, Lian notes that, while 500 protein spots were observed, only 28 of them could be specifically identified based on their molecular weight and pI. (See Lian, page 520, second column).

Furthermore, of the 28 proteins listed in Table 6, only one has an mRNA level measured by microarray which is differentially expressed according to the authors (spot 7: melanoma X-actin, which mRNA changed from 2539 to 341.3, and protein changed from 1 to 3). None of the other mRNAs listed in Table 6 show a significant change in expression level when using the criteria established by the authors for the less sensitive microarray technique.

There is also one gene in Table 6 whose expression was measured by the more sensitive technique of DD, and its level increased from a qualitative value of 0 to 2, a more than 2-fold increase (spot 2: actin, gamma, cytoplasmic). This increase in mRNA was accompanied by a corresponding increase in protein level, from 3 to 6.

Therefore, although the authors characterize the mRNA and protein levels as having a "poor correlation," this does not reflect a lack of a correlation between a change in mRNA level and a corresponding change in protein level. Only two genes meet the authors' criteria for differentially expressed mRNA level, and of those, one apparently shows a corresponding change

in protein level and one does not. *Id.* at 521, Table 6. Thus, this reference does not contradict Applicants' position that, in general, a change in mRNA level corresponds to a change in the level of the encoded polypeptide.

With respect to the Fessler reference, Applicants note that the discrepancy between the number of genes which were upregulated in human neutrophils which were exposed to bacterial LPS and the number of proteins identified as being upregulated to a statistically significant degree is a consequence of the difficulty of identifying polypeptides by two dimensional gel electrophoresis and does not reflect a lack of correlation between differential mRNA expression and differential expression of the encoded polypeptide. In particular, Fessler notes that, while 1200 protein spots were evident on each PH 3.0-10.0 gel, only 125 of them matched on all 12 gels. (See Fessler, page 31,293, first and second paragraphs in the second column).

Furthermore, Fessler lists in Table VIII a comparison of the change in the level of mRNA for 13 up-regulated proteins and 5 down-regulated proteins. Of the 13 up-regulated proteins, a change in mRNA levels is reported for only 3 such proteins. For these 3, mRNA levels are increased in 2 and decreased in the third. Of the 5 down-regulated proteins, a change in mRNA is reported for 3 such proteins. In all 3, mRNA levels also are decreased. Thus, in 5 of the 6 cases for which a change in mRNA levels are reported, the change in the level of mRNA corresponds to the change in the level of the protein. This is consistent with Applicants assertion that a change in the level of mRNA for a particular protein generally leads to a corresponding change in the level of the encoded protein.

Regarding the remainder of the proteins listed in Table VIII, in 6 instances, protein levels changed while mRNA levels were unchanged. This evidence has no relevance to Applicants' assertions of the influence that changes in mRNA levels have on protein levels. In explaining these instances, Fessler explains that LPS has post-transcriptional activity that can influence protein levels (Fessler at 31300, right column). Nothing in these results by Fessler suggests that a change in the level of mRNA for a particular protein does not generally lead to a corresponding change in the level of the encoded protein. Accordingly, these results are not contrary to Applicants assertions.

The Examiner asserts that the Orntoft reference submitted by Applicants indicates that it was only possible to compare mRNA and protein alterations in relatively few cases of well

focused abundant proteins) and that, although mRNA and protein levels showed a striking correspondence, there were discrepancies that may be attributed to translational regulation, post-translational processing, protein degradation, or a combination of thereof. The Examiner also maintains that the Orntoft and Futcher references relate to abundantly expressed polypeptides. The Examiner asserts that Orntoft suggests that both transcript and protein levels need to be analyzed. According to the Examiner, Applicants have not provided any testing of PRO1864 polypeptide expression and there is no evidence of record that either PRO1864 mRNA or PRO1864 polypeptide is abundantly expressed in either tumor tissue or normal tissue.

Applicants maintain that Orntoft demonstrates a high correlation between differential mRNA expression and differential expression of the encoded polypeptide. In particular, the authors found a correlation in 39 of the 40 genes examined. Likewise, Futcher found "a good correlation between protein abundance, mRNA abundance, and codon bias." *Futcher et al.* at Abstract. While Applicants acknowledge that transcriptional regulation is not the sole mechanism for regulating gene expression, as discussed above and previously submitted, Applicants maintain that transcription is the predominant point of regulation. Furthermore, Applicants maintain that, in general, differential mRNA expression correlates with differential expression of the encoded polypeptide. Applicants have submitted numerous references which support the correlation between changes in mRNA levels and changes in the levels of the encoded polypeptides. Applicants maintain that the correlation between differential mRNA expression and differential expression of the encoded polypeptide is not limited to abundantly expressed polypeptides but rather is characteristic of differentially expressed proteins in general. In addition, Applicants maintain that, in view of the correlation between differential mRNA expression and differential expression of the encoded polypeptide, it is more likely than not that the PRO1864 polypeptide is differentially expressed in melanoma.

Applicants' Evidence Establishes that a Change in mRNA Level for a Particular Gene leads to Corresponding Change in the Level of the Encoded Protein

In support of the assertion that changes in mRNA for a particular gene are positively correlated to changes in the corresponding protein level, Applicants previously submitted a copy of a second Declaration by J. Christopher Grimaldi, two Declarations by Paul Polakis, Ph.D.,

excerpts from the Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (3rd ed. 1994) and (4th ed. 2002), excerpts from the textbook, Genes VI, (Benjamin Lewin, Genes VI (1997)), a reference by Zhigang *et al.*, World Journal of Surgical Oncology 2:13, 2004, and a reference by Meric *et al.*, Molecular Cancer Therapeutics, vol. 1, 971-979 (2002). In addition, in the most recent response, Applicants submitted over 100 additional references in support of their assertion that changes in mRNA for a particular gene are positively correlated to changes in the corresponding protein level. The details of the teachings of these declarations and references, and how they support Applicants' asserted utility, are of record and will not be repeated here.

With respect to the second Polakis Declaration, the Examiner asserts "The data presented in Exhibit B merely scores mRNA and protein levels as either '+' or '-' which is insufficient to support Applicants' assertion that an increase in mRNA levels corresponds with an increase in the level of the corresponding protein. While the Polakis Declaration refers to being able to quantitatively measure mRNA and protein levels in both tumor tissue and normal tissue, this data is not supplied. Exhibit B does not quantitatively measure both mRNA and protein levels in both tumor tissue and normal tissue and the significance of the symbols '+' and '-' is not clear." *Office Action* at 10.

The case law has clearly established that in considering affidavit evidence, the Examiner must consider all of the evidence of record anew. *In re Rinehart,* 531 F.2d 1084, 189 USPQ 143 (C.C.P.A. 1976) and *In re Piasecki,* 745 F.2d. 1015, 226 USPQ 881 (Fed. Cir. 1985). "After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of argument." *In re Alton,* 37 U.S.P.Q.2d 1578, 1584 (Fed. Cir. 1996)(quoting *In re Oetiker,* 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992)). Furthermore, the Federal Court of Appeals held in *In re Alton*, "We are aware of no reason why opinion evidence relating to a fact issue should not be considered by an examiner." *Id.* at 1583. Applicants also respectfully draw the Examiner's attention to the Utility Examination Guidelines which state, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely

because of a disagreement over the significance or meaning of the facts offered." *Utility Examination Guidelines Part IIB*, 66 Fed. Reg. 1098 (2001).

In addition, M.P.E.P §716.01 provides that "Where the evidence [in a Declaration] is insufficient to overcome the rejection, the Examiner must specifically explain why the evidence is insufficient. General statements such as 'the declaration lacks technical validity' or 'the evidence is not commensurate with the scope of the claims' without an explanation supporting such findings are insufficient."

The PTO's assertion that "Exhibit B does not quantitatively measure both mRNA and protein levels in both tumor tissue and normal tissue" is directly contradictory to Dr. Polakis' statement that "To date, we have successfully generated antibodies that bind to 31 of the tumor antigen proteins expressed from these differentially expressed gene transcripts and have used these antibodies to quantitatively determine the level of production of these tumor antigen proteins in both human tumor tissue and normal tissue. We have then quantitatively compared the level of mRNA and protein in both the tumor and normal tissues analyzed." *Second Declaration of Dr. Polakis, ¶4* Thus, Dr. Polakis measured the level of mRNA and protein in normal and tumor samples and compared the levels in each to assess whether the mRNAs and polypeptides were differentially expressed. Applicants maintain that the PTO's unsupported rejection of the Declaration is improper in view of the requirements of M.P.E.P §716.01.

Likewise, the PTO's assertion that "The significance of the symbols '+' and '-' is not clear" is directly contradictory to Dr. Polakis' statement that "In Exhibit B, '+' means that the mRNA or protein was detectably overexpressed in the tumor tissue relative to the normal tissue..." *Second Declaration of Dr. Polakis, ¶4.* Thus, Dr. Polakis explains the significance of the data in Exhibit B in his Declaration. Again, Applicants maintain that the PTO's unsupported rejection of the Declaration is improper in view of the requirements of M.P.E.P §716.01. Furthermore, Applicants maintain that the "+" or "-" designations in Exhibit B are sufficient to demonstrate the utility of the claimed invention and that there is no requirement that the data be provided in a numerical format.

The Examiner also asserts that "Exhibit B does not measure the levels of PRO1864 mRNA levels and PRO1864 polypeptide levels in melanomas and normal skin and there are examples of genes for which such a correlation does not exist. Again, the Polakis declaration

(Exhibit 3, 5/2/2005) teaches that -20% of the samples examined do not show a correlation between an increase in the level of mRNA and an increase in the level of the encoded protein (paragraph 5)." *Office Action* at 10. In response, Applicants maintain that, although the Polakis Declarations do not contain an analysis of the PRO1864 polypeptide, they demonstrate that, in general, differential mRNA expression correlates with differential expression of the encoded polypeptide. As previously submitted, 35 U.S.C. §101 does not require that utility be demonstrated with absolute certainty. Rather, the standard is whether the demonstration of utility is sufficient to prove that it is **more likely than not** that a person of skill in the art would be convinced, **to a reasonable probability,** that the asserted utility is true. Accordingly, the demonstration that, in general, differential mRNA expression correlates with differential expression of the encoded polypeptide also demonstrates that it is more likely than not that the PRO1864 polypeptide is differentially expressed.

In addition to the foregoing arguments, Applicants also submit herewith a copy of a declaration by Randy Scott, Ph.D. (attached as Exhibit 1). Dr. Scott is an independent expert in the field of molecular diagnostics, with over 15 years of experience. He is the author of over 40 scientific publications in the fields of protein biology, gene discovery, and cancer, and is an inventor on several issued patents. His curriculum vitae is attached to the declaration. In paragraph 10 of his declaration, Dr. Scott states:

> One reason for the success and wide-spread use of the DNA microarray technique, which has led to the emergence of a new industry, is that generally there is a good correlation between mRNA levels determined by microarray analysis and expression levels of the translated protein. Although there are some exceptions on an individual gene basis, it has been a consensus in the scientific community that elevated mRNA levels are good predictors of increased abundance of the corresponding translated proteins in a particular tissue. Therefore, diagnostic markers and drug candidates can be readily and efficiently screened and identified using this technique, without the need to directly measure individual protein expression levels. *Scott Declaration* at ¶10 (emphasis added).

Applicants submit the opinion of yet another expert in the field that changes in mRNA level for a particular protein in a given tissue generally lead to a corresponding change in the level of the encoded protein. Importantly, Dr. Scott also states that, contrary to the contentions of the PTO, diagnostic markers can be identified "without the need to directly measure individual protein expression levels." This opinion is supported by Dr. Scott's extensive experience in the field, as

well as the fact that an entire industry has developed around technology to assess differential mRNA expression. As stated previously, there would be little reason to study changes in mRNA expression levels if those changes did not result in corresponding changes in the encoded protein levels.

In summary, Applicants have provided the Declaration of Dr. Scott in addition to the declarations and references already of record which support Applicants' asserted utility, either directly or indirectly. These references support the assertion that in general, a change in mRNA expression level for a particular gene leads to a corresponding change in the level of expression of the encoded protein. As Applicants have previously acknowledged, the correlation between changes in mRNA level and protein level is not exact, and there are exceptions. However, Applicants remind the PTO that the asserted utility does not have to be established to a statistical certainty, or beyond a reasonable doubt. *See M.P.E.P.* at § 2107.02, part VII (2004). Therefore, the fact that there are exceptions to the correlation between changes in mRNA and changes in protein does not provide a proper basis for rejecting Applicants' asserted utility. Applicants submit that considering the evidence as a whole, with the overwhelming majority of the evidence supporting Applicants' asserted utility, a person of skill in the art would conclude that Applicants' asserted utility is "more likely than not true." *Id.*

In conclusion, Applicants submit that they have offered sufficient evidence to establish that it is more likely than not that one of skill in the art would believe that, because the PRO1864 mRNA is differentially expressed in melanoma, the PRO1864 polypeptide will likewise be differentially expressed in melanoma. This differential expression of the PRO1864 polypeptide makes the claimed antibodies useful as diagnostic tools for cancer, particularly melanoma.

The PTO's Position is Inconsistent with the Utility Guidelines and the Courts

In response to Applicants' evidence and arguments, the PTO takes the position that Applicants must present specific evidence directly demonstrating the utility of the claimed antibodies – specifically, direct evidence of differential expression of PRO1864 polypeptide in tumor and normal tissue. Applicants submit that this requirement is inconsistent with the Utility Guidelines and the courts.

In response to the over 100 supporting references submitted in Applicants' previous response, the PTO makes the following conclusory argument:

> Exhibits 1-22 (5/1/2006) have been considered. However, none of this evidence discloses anything specific regarding PRO1568 [*sic*] mRNA expression, PRO1568 [*sic*] polypeptide expression, or the correlation between the two in normal tissue and tumor tissue. The exhibits do not provide any data concerning PRO1568 [*sic*] mRNA expression, PRO1568 [*sic*] polypeptide expression, or the correlation between the two in tumor tissue and normal tissue. The fact that there may be a commonly understood general rule or dogma that increased mRNA levels are predictive of corresponding increased levels of the encoded protein does not establish the correlation between the change, if any, in PRO1864 transcripts and PRO1864 polypeptide expression in tumors because there are examples of genes for which such a correlation does not exist, as evidenced by the Polakis declaration (Exhibit 3, 5/2/2005). *Office Action* at 14.
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> The specification does not establish if the disclosed change in PRO1864 mRNA expression is one of those cases where this is a correlation between a change in mRNA level and a corresponding change in the level of the encoded protein. Applicants have not provided any testing of PRO1864 polypeptide expression... The correlation between the disclosed change in PRO1864 mRNA and a change in PRO1864 polypeptide expression is unknown and is not disclosed. *Office Action* at 14-15 (emphasis added).
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> Neither the specification nor any of Applicants' arguments, exhibits, declarations or other evidence provide any specific data disclosing if or how PRO1864 polypeptide expression changes in tumor tissue. Instead, Applicants rely on a general correlation between mRNA expression and expression of the encoded protein rather than the specific correlation between PRO1864 transcripts and PRO1864 polypeptide expression to argue that it is more likely than not that a change in PRO1864 transcripts is correlated with an assumed change in PRO1864 polypeptide expression. Applicants' arguments, exhibits and declarations only show that it is not implausible that invention will work for its intended purpose. Without any evidence of the expression of PRO1864 in tumor tissue one skilled in the art would be required to do further research to determine whether or not the PRO1864 protein expression correlates with PRO1864 mRNA levels in melanomas compared to normal skin. *Office Action* at 15-16 (emphasis added).

Thus, the PTO implies the following argument: (1) the evidence of record demonstrates that there are exceptions to the general rule that increased mRNA levels correspond to increased

levels of the encoded polypeptide; (2) because such exceptions exist, it is mandatory that specific data of differential PRO18644 polypeptide expression in melanoma as compared to normal skin tissue be disclosed; and (3) since such is not disclosed, the claimed antibodies that bind the PRO1864 polypeptide have no substantial utility.

Adopting the PTO's standard for utility would result in a per se rule that a difference in mRNA expression cannot establish a utility for the encoded polypeptide and antibodies thereto. Thus, the PTO chooses to heighten the utility requirement to require specific, direct evidence of utility when there are exceptions to a generally accepted rule that is relied upon for utility. This heightened utility requirement is inconsistent with the Utility Guidelines and the courts. There is no requirement that utility be dispositively proven:

> Furthermore, the applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." *In re Irons,* 340 F.2d 974, 978, 144 USPQ 351, 354 (CCPA 1965) ... Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. *M.P.E.P.* 2107.02 VII (emphasis in original).

Nor is there requirement that only direct evidence of utility is sufficient to establish utility. Instead, it is established that indirect evidence that is reasonably indicative of utility is sufficient to fulfill the requirements of 35 U.S.C. §101. *Nelson v. Bowler*, 626 F.2d 853, 856. Furthermore, there is no requirement that indirect evidence necessarily and always prove actual utility. Instead, there only need be a reasonable correlation between the indirect evidence and the asserted utility. *Id.* at 857, *Cross v. Iizuka*, 753 F.2d 1040, 1050-1051. The indirect evidence need not absolutely prove the asserted utility. All that is required is that the tests be reasonably indicative of the asserted utility. In other words, there need only be a sufficient correlation between the indirect evidence and the utility so as to convince those skilled in the art, to a reasonable probability, that the novel compound will possess the asserted utility. *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564.

The PTO appears to consider the above guidance from the courts inapplicable to the present situation because in those cases the claimed compound had been tested, and, in the present test, the polypeptides to which the claimed antibodies specifically bind have not been tested. However, the PTO's position fails to recognize the issue in question for the above cases.

The issue in question was whether or not Appellants' evidence (*in vitro* or animal testing of compound), which was different in nature from the asserted utility (therapeutic use of compound), was sufficient to fulfill the requirements of 35 U.S.C. §101 when there was a reasonable link between Appellants' evidence and the asserted utility. In the present case, Applicants submit that their evidence (differential mRNA expression) is reasonably linked to the asserted utility (diagnostic use of the encoded polypeptide). Insofar as it is uncontested that differential mRNA expression is reasonably linked to differential polypeptide expression, Applicants submit that such linkage is sufficient to fulfill the requirements of 35 U.S.C. §101 as provided by the guidance of the Utility Guidelines and the courts.

In conclusion, the PTO's heightened requirement for establishing utility of the presently claimed antibodies is contrary to the Utility Guidelines and the courts: it is sufficient to present evidence of differential mRNA expression since it is understood in the art that differential mRNA expression is reasonably linked to differential polypeptide expression. As discussed above, even if the PTO has presented evidence that changes in mRNA expression is not always correlated with changes in protein expression, Applicants' overwhelming rebuttal evidence is more than sufficient to establish that changes in mRNA level typically lead to corresponding changes in protein level. As such, Applicants have established that it is more likely than not that one of skill in the art would believe that because the PRO1864 mRNA is differentially expressed in melanoma as compared to normal skin tissue, the PRO1864 polypeptide will likewise be differentially expressed in melanoma. Accordingly, when the evidence is applied to the proper standard for utility, it is clear that this differential expression of the PRO1864 polypeptide establishes the claimed antibodies useful as diagnostic tools for cancer, particularly melanoma.

Specific Utility

The Asserted Substantial Utilities are Specific to the Claimed Antibodies

Applicants next address the PTO's assertion that the asserted utilities are not specific to the claimed antibodies related to PRO1864. Applicants respectfully disagree.

Specific utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the

PRO1864 gene and polypeptide in melanoma, along with the declarations and references discussed above, provide a specific utility for the claimed antibodies.

As discussed above, there are significant data which show that it is more likely than not that the PRO1864 polypeptide is differentially expressed in melanoma as compared to normal skin tissue. These data are strong evidence that the PRO1864 polypeptide is associated with melanoma. Thus, contrary to the assertions of the PTO, Applicants submit that they have provided evidence associating the PRO1864 polypeptide with a specific disease. The asserted utility as a diagnostic tool for cancer, particularly melanoma, is a specific utility – it is not a general utility that would apply to the broad class of antibodies.

Conclusion

Applicants remind the PTO that the evidence supporting utility does not need to be direct "specific" evidence, nor does it need to provide an exact correlation between the submitted evidence and the asserted utility. Instead, evidence which is "reasonably" correlated with the asserted utility is sufficient. *See Fujikawa v. Wattanasin*, 93 F.3d 1559, 1565, 39 U.S.P.Q. 2d 1895 (Fed. Cir. 1996) ("a 'rigorous correlation' need not be shown in order to establish practical utility; 'reasonable correlation' suffices"); *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739 (Fed. Cir. 1985) (same); *Nelson v. Bowler*, 626 F.2d 853, 857, 206 U.S.P.Q. 881 (C.C.P.A. 1980) (same). In addition, utility need only be shown to be "more likely than not true," not to a statistical certainty. *M.P.E.P.* at § 2107.02, part VII (2004). Considering the evidence as a whole in light of the relevant standards for establishing utility, Applicants have established at least one specific, substantial, and credible utility. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Enablement

The PTO maintains its rejection of Claims 1-5 under 35 U.S.C. § 112, first paragraph. Specifically, the PTO asserts that because the claimed invention is not supported by either a specific or substantial asserted utility or a well-established utility, one skilled in the art would not know how to use the claimed invention.

Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed antibodies.

Thus, since the enablement rejection is based on the rejection of the claims as lacking utility, Applicants respectfully request that the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. §112.

Title of the Application

The Examiner asserted that the title of the application is not indicative of the subject matter being claimed. Applicants have amended the title to address the Examiner's concerns.

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: Oct. 10, 2006

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